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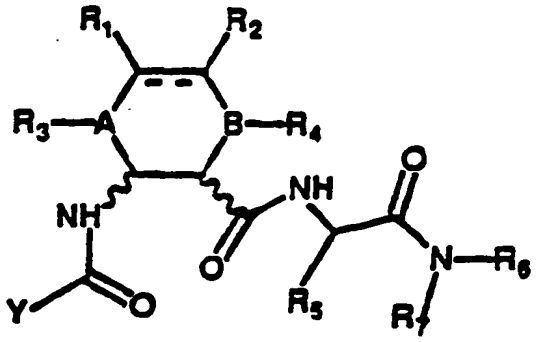
(54) Title: TACHYQUININE ANTAGONISTS, THEIR PREPARATION AND USE IN PHARMACEUTICAL FORMULATIONS

(57) Abstract

A description is given of tachyquinine antagonists having general formula (I), their preparation and use in pharmaceutical formulations.



(I)

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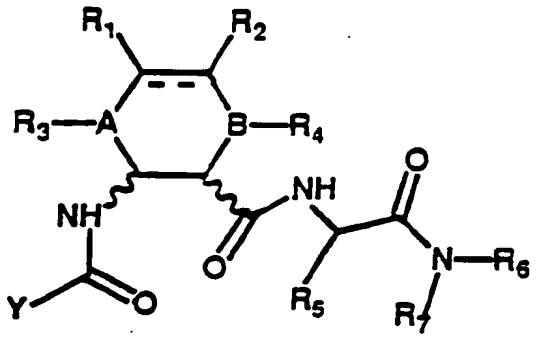
TACHYQUININE ANTAGONISTS, THEIR PREPARATION AND USE IN PHARMACEUTICAL FORMULATIONS

Field of the invention

The present invention refers to tachyquinine antagonists, their preparation and use in pharmaceutical formulations.

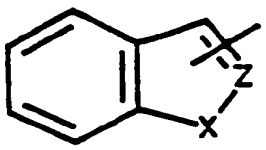
In particular, the present invention refers to compounds having general formula (I)



(I)

wherein:

Y is selected out of a group consisting of hydrogen, a linear or branched alkyl radical containing 1 to 6 carbon atoms, a linear or branched alkenyl radical containing 2 to 7 carbon atoms, a linear or branched alkynyl radical containing 3 to 7 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, possibly substituted with at least one atom selected out of a group consisting of N, S, and O, an aryl-, aryl-alkyl-, alkyl-aryl- radical containing 7 to 12 carbon atoms, a radical of type



wherein X stands for O, S, CH_2, NH or N-R_8 where R_8 is selected out of a group consisting of H, a linear or branched alkyl radical containing 1 to 6 carbon atoms, a linear or branched alkenyl radical containing 2 to 7 carbon atoms, a linear or branched alkynyl radical containing 3 to 7 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, possibly substituted with at least one atom selected out of a group consisting of N, S, and O, an aryl-, aryl-alkyl-, alkyl-aryl- radical containing 7 to 12 carbon atoms, and Z = CH or N, each with suitable substituents;

symbol --- represents a single or a double bond: if the bond is single, R_1 and R_2 are selected out of a group consisting of hydrogen, hydroxyl and halogen or are joined to form an epoxide; if the bond is double, they are hydrogen or halogen; A and B stand for N or CH; R_3 and R_4 are selected out of the group consisting of hydrogen, a linear or branched alkyl radical containing 1 to 6 carbon atoms, a linear or branched alkenyl radical containing 2 to 7 carbon atoms, a linear or branched alkynyl radical containing 3 to 7 carbon atoms, or are joined together to form a -$(CH_2)_n$- bridge, where n stands for a whole number from 1 to 3;

R_5 stands for an alkyl-, aryl-, aryl-alkyl- or alkyl-aryl- radical with 15 carbon atoms max.;

R_6 and R_7 are selected out of a group consisting of hydrogen, an alkyl -, aryl-, aryl-alkyl- or alkyl-aryl- radical as defined above.

Symbol ~~~ means that the configuration of the asymmetric carbon atoms of 2-amino-cyclohexanecarboxylic acid is S or R.

Tachyquinine antagonist compounds as per formula (I) prove to be effective in the treatment of diseases where tachyquinines play a pathogenic role, in particular in the treatment of arthritis, asthma, inflammations, tumoral growth, gastrointestinal hypermotility, Huntington's disease, neuritis, neuralgia, migraine, hypertension, incontinence of urine, urticaria, carcinoid syndrome symptoms, influenza, and cold.

State of the art

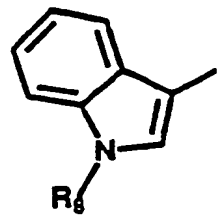
Tachyquinines are a family of three peptides at least, known as substance P (SP), neuroquinine A (NKA) and neuroquinine B (NKB). Research in the field of tachyquinine antagonists, initially directed toward single or multiple replacement of amino acids of the peptide agonists sequence of Substance P and of the other tachyquinines, brought to the discovery of nonapeptides containing one or more D-tryptophan units [Regoli et al., Pharmacol., 28, 301 (1984)].

On the other hand, the problems related to the use of high-molecular-weight peptides as drugs (multiplicity of enzymatic hydrolytic attack sites, poor bioavailability, rapid excretion from the liver and kidneys) spurred to search for the minimum peptide fragment still capable of exerting an antagonist action. These studies brought to the singling out of suitably derivatized SP antagonists tripeptides and dipeptides (European patents Nos. 333174 and 394989).

Detailed description of the invention

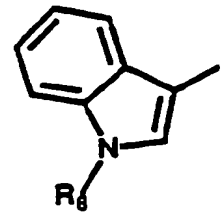
It has surprisingly been found - and this finding constitutes a fundamental feature of the present invention - that non-peptidic compounds of general formula (I) as defined above are good inhibitors of the tachyquinines bond to NK1 receptor and have a sufficient metabolic stability.

A preferred group of compounds under the present invention includes compounds of formula (I) wherein:

Y = 

and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, A, and B are as defined above.

A particularly preferred products are compounds of general formula (I) wherein:

Y = 

and R_8 = H, R_5 and R_6 = 

The present description sets forth the following substituent groups as particularly preferred:

the alkyl radical is selected out of a group consisting of methyl, ethyl, propyl, butyl, and pentyl; the alkenyl radical is selected out of the group consisting of propenyl and butenyl; the alkynyl radical is propynyl; possibly substituted aryl-, alkyl-aryl- and aryl-alkyl- radicals present preferably an alkyl radical as defined above, while the aryl moiety is preferebly possibly substituted pyridine, benzofuran, benzene, indole, naphthyl, tetrahydroquinoline, imidazole, tetrahydroindoline; a cycloalkyl radical, possibly substituted at least with an atom selected out of a group consisting of N, S and O, is preferably selected out of a group consisting of cyclohexane, cyclopentane, cycloheptane, cyclooctane, piperidine, morpholine, piperazine, and pyrazine.

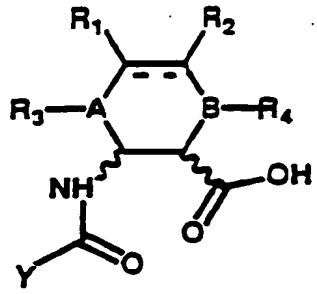
In view of the asymmetry centres of formula (I), this invention refers to the various diastereoisomers of said formula; in particular, substituent R_5 is preferably in S-position.

The compounds under the present invention proved to be SP, Neuroquinine A, and Neuroquinine B antagonists. Therefore, they can be utilized for the prevention and treatment of diseases where tachyquinines (SP, NKA, NKB) play a neuromodulating role, such as respiratory conditions (e.g. asthma, allergic rhinitis), ophthalmic conditions (e.g. conjunctivitis), cutaneous conditions (e.g. allergic dermatitis, dermatitis by contact, psoriasis), intestinal conditions (e.g. ulcerative colitis, Crohn's disease).

Another fundamental object of the invention is the preparation of compounds of formula (I) by condensation.

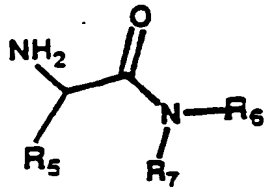
Compounds of general formula (I) as defined above are prepared via the steps of:

a) condensing, in the presence of a suitable condensing agent, intermediate of formula (II)



(II)

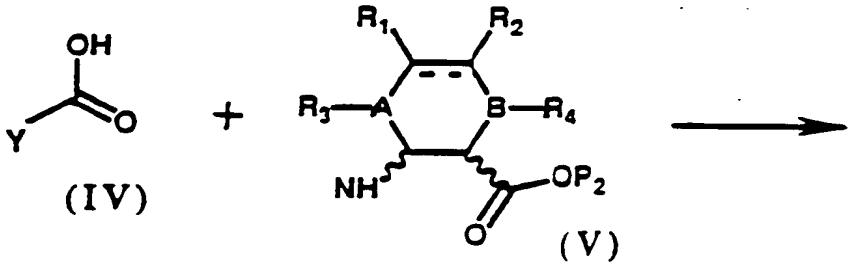
with intermediate of formula (III)

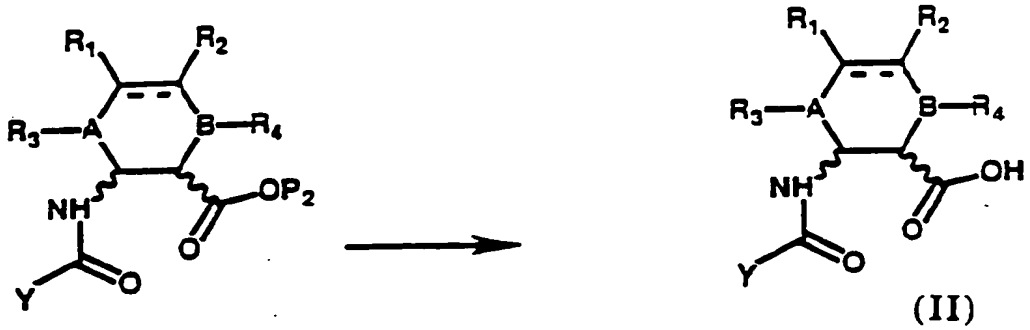


(III)

where R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, A, and B are as defined above, said compound of formula (II) being prepared by condensation, in the presence of a suitable condensing agent, of a compound of general formula (IV) with a derivative of the acid of general formula (V), suitably substituted on the ring and possibly protected on the

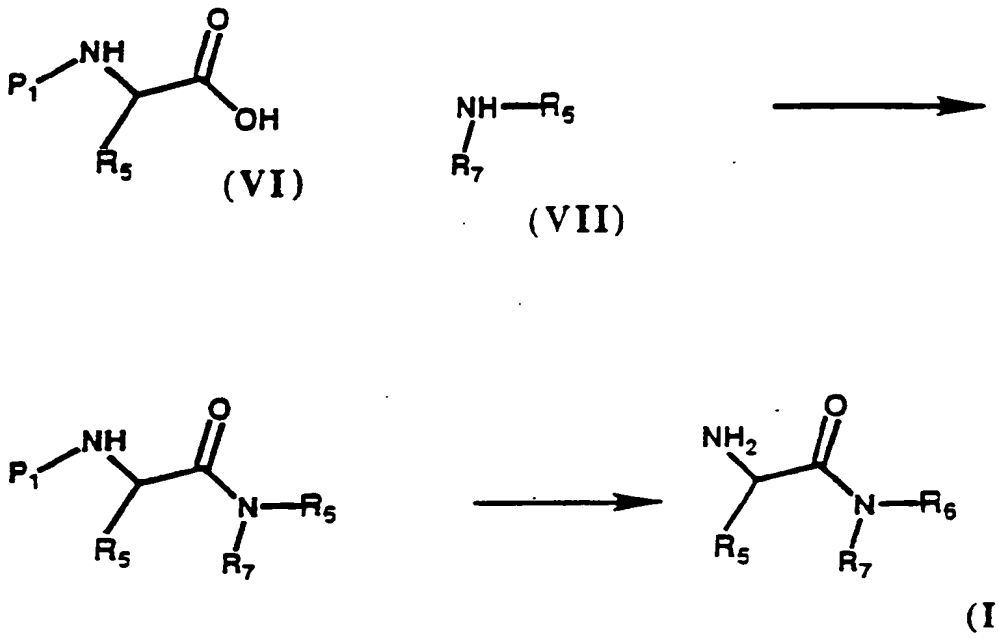
hydroxyl group of the ring by a group of the tert-butyl type, followed by elimination of the carboxylic end group





where R_1, R_2, R_3, R_4, R_8, A, and B are as defined above and P_2 is a group that temporarily protects the carboxylic group, in particular the ester used is a methyl ester and the successive carboxyl elimination is carried out by basic hydrolysis,

and intermediates of general formula (III) being prepared by condensation of amino acid derivative of general formula (VI) and amine of general formula (VII)



(VI) (VII) (III)

where R_5, R_6, R_7 are as defined above and P_1 is a group protecting the α-amino group, selected out of the groups commonly used in classical peptide syntheses, which can be easily removed under conditions not causing the partial or total opening of the bond between R_6, R_7 and nitrogen. In particular, P_1 is preferably a tert-butyloxycarbonyl or fluorenylmethyloxycarbonyl group and can be removed by acidolysis or basic treatment, respectively, wherein the benzyl groups, if any, bound to the substituted amide are stable, said condensation being carried out at room temperature in the presence of aprotic polar organic solvents capable of solubilizing the reagents and not negatively interfering with the reaction progress;

b) eliminating the reaction by-products by evaporation of the reaction solvent and treatment of the residue, or a solution of same in a suitable organic solvent, with slightly acid or slightly basic aqueous solutions;

c) separating the residue obtained under b) by chromatography or crystallization.

The reaction solvents mentioned under a) and b) are selected out of the group consisting of dimethylformamide, dioxane, tetrahydrofuran, halogenated aliphatic hydrocarbons, methylene chloride, dichloroethane.

Excellent product yield and purity were obtained using benzotriazolyloxy tripyrrolidine phosphonium hexafluorophosphate (PyBop) as a condensing agent. In particular, the reaction was carried out by addition of slight excess of PyBop to a carboxylic component (formula II) solution, maintained at low temperature, followed by addition of the aminic component hydrochloride (formula VI) and a quantity of tertiary amine of three equivalents in respect of the condensing agent.

An alternative procedure envisages the use, as a condensing agent, of 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide.

A further object of the present invention is the synthesis procedure of intermediate of general formula (II) and the product obtained therefrom (intermediate II).

The compounds of this invention can exist in different isomeric configurations. In fact, the configuration of the carbon atom bound

to substituent R_5 is univocally determined by the synthesis starting compound being of formula VI. However, the other starting compound (i.e. 2-aminocyclohexanecarboxylic acid as per formula II) has 2 asymmetric carbon atoms and usually consists of an inseparable mixture of two enantiomers, whose ring substituents are either cis or trans. It follows that the compounds of this invention are mixtures of diastereoisomers (two having trans ring substituents and two having cis substituents). Said mixtures can be easily resolved by chromatography. In any case, compounds of formula (I) can be used both in optically active form and in the form of isomeric mixtures. The following examples illustrate some embodiments of the claimed invention and the synthesis procedure thereof.

EXAMPLE 1

N-methyl-N-benzylamide of N^{α}-{[N(indolin-3-yl-carbonyl)(R,R)-trans-2-amino]cyclohexanoyl}-L-phenylalanine and N-methyl-N-benzylamide of N^{α}-{[N(indolin-3-yl-carbonyl)(L,L)-trans-2-amino]cyclohexanoyl}-L-phenylalanine

1) Methyl ester hydrochloride of trans-2-amino-cyclohexanecarboxylic acid (HCl,H-trans-2-Ac^6c-OMe)

(Abbreviations 2-Ac^6c stands for 2-amino cyclohexanecarboxylic acid and I3c means the indolin-3-yl-carbonyl residue).

Trans H-2-Ac^6c-OH (500 mg) was suspended, at room temperature, in a saturated solution of hydrochloric acid in methyl alcohol (7.5 ml). After 24-hr stirring at room temperature the solution was limpid.

The resulting solution was evaporated to dryness by nitrogen blowing; the residue was repeatedly taken up with methyl alcohol (4 x 15 ml) and evaporated to dryness for excess hydrochloric acid elimination.

The product was isolated by grounding with diethyl ether (3 x 10 ml). Obtained 648 mg.

The R_f value obtained by thin layer chromatography (TLC) (eluent: chloroform/methanol/acetic acid (CMA), 85/10/5) was 0.25.

2) Methyl ester of N-(indolin-3-yl-carbonyl)-trans-2-amino-cyclohexanecarboxylic acid (I3c-trans-2-Ac^{6}c-OMe)

A suspension of the product obtained under 1) (500 mg) in dichloromethane (DCM) (5 ml) was cooled to 0°C, stirred under nitrogen atmosphere, and added with 402 mg indolyl-3-carboxylic acid (I3c-OH), 337 mg 1-hydroxy-benzotriazole (HOBt), 488 mg 1-ethyl-3-(3'-dimethylamino propyl)carbodiimide (WSC), and 0.52 ml diisopropylethylamine (DiPEA). The limpid solution was allowed to stir for 45 min at 0°C and for additional 16 hrs at room temperature. The solvent was eliminated by evaporation under reduced pressure and the residue was taken up with ethyl acetate (EtOAc) (50 ml). The organic solution was extracted with a 5% $NaHCO_3$ aqueous solution (3 x 50 ml), with an NaCl saturated aqueous solution (3 x 50 ml), with a 0.1 N HCl aqueous solution (3 x 50 ml), and again with an NaCl saturated aqueous solution (3 x 50 ml). The organic phase, after water elimination on Na_2SO_4, was evaporated to dryness to give a white powder (583 mg, yield 78%).

HPCL was carried out with 5 mm Spherisorb® ODS-2 (150 x 4.6 mm) column eluting with:

A = 0.1% trifluoroacetic acid in acetonitrile;

B = 0.1% trifluoroacetic acid in water;

gradient outline 20% to 80% of A at 25 min;

flow rate 1 ml/min; effluent monitored at 230 nm (UV detector).

HPLC analysis showed a single peak at retention time (R_t) = 15.83 min.

The R_f value obtained by thin layer chromatography (TLC) (eluent: ethyl acetate/hexane, 80/20 v/v) was 0.31.

3) N-(indolin-3-yl-carbonyl)-trans-2-amino-cyclohexanecarboxylic acid (I3c-trans-2-Ac^{6}c-OH)

A suspension of the product obtained under 2) above (500 mg) in 5% NaOH (9 ml) was allowed to stir for 36 hrs at room temperature. The limpid solution was maintained at 0°C and under vigorous stirring, extracted with EtOAc (15 ml x 3) and acidified with 0.1 N HCl to pH 3.

The product was isolated by filtering the precipitate that forms and drying under reduced pressure (402 mg, yield 84%).

The R_f value obtained by thin layer chromatography (TLC) (eluent: chloroform/methyl alcohol (CM), 80/20 v/v) was 0.29.

HPLC analysis as per step 2 showed a single peak at R_t = 12.96 min.

4) N-methyl-N-benzyl amide of N(tert-butyloxycarbonyl)-L-phenylalanine (Boc-Phe-NMeBz)

A solution of N-(tert-butyloxycarbonyl)-L-phenylalanine (5 g) in anhydrous dichloromethane (10 ml) was vigorously stirred at 0°C under nitrogen atmosphere, added with N-methyl-N-benzylamine (2.66 ml), bromotripyrrolidinephosphonium hexafluorophosphate (PyBroP), and slowly with DiPEA (6.55 ml). The solution was allowed to stir for 30 min at 0°C and for additional 4 hrs at room temperature. The solvent was eliminated by evaporation under reduced pressure and the residue was taken up with EtOAc (50 ml).

The organic solution was extracted with a 5% $NaHCO_3$ aqueous solution (3 x 50 ml), with an NaCl saturated aqueous solution (3 x 50 ml), with a 0.1 N HCl aqueous solution (3 x 50 ml), and again with an NaCl saturated aqueous solution (3 x 50 ml). The organic phase, after water elimination on Na_2SO_4, was evaporated to dryness to give a pale yellow oil, which was crystallized from 20 ml ethanol/water mixture (50/50 v/v). The product was isolated by filtering the precipitate and drying under reduced pressure (4.86 g, yield 70%). HPLC analysis as per step 2, showed a single peak at R_t = 24.11 min. The R_f value obtained by thin layer chromatography (TLC) (eluent: CM, 90/10 v/v) was 0.80.

5) N-methyl-N-benzyl amide hydrochloride of L-phenylalanine (HCl H-Phe-NMeBz)

A suspension of the product obtained under 4) above (1.0 g) in ca. 2N HCl saturated EtOAc solution was allowed to stir for 2 hrs at room temperature. The solvent was eliminated by slight nitrogen blowing and the residue was repeatedly suspended with ethyl ether (4

x 30 ml) and evaporated to dryness. The product obtained was a white powder (0.669 g, yield 80%).

The R_f value obtained by thin layer chromatography (TLC) (eluent: CM) was 0.68.

HPLC analysis as per step 2 showed a single broad peak at R_t = 16.03 min.

6) N-methyl-N-benzylamide of N^{α} -{[N(indolin-3-yl-carbonyl)(R,R)-trans-2-amino]cyclohexanoyl}-L-phenylalanine

and N-methyl-N-benzylamide of N^{α}-{[N(indolin-3-yl-carbonyl)(L,L)-trans-2-amino]cyclohexanoyl}-L-phenylalanine

A suspension of the product obtained under 3) above (50 mg) in DCM (5 ml) was cooled to 0°C, allowed to stir under nitrogen atmosphere and added with the product obtained under 5) above (52 mg), benzotriazolyloxy tripyrrolidine phosphonium hexafluorophosphate (PyBop) (106 mg) and DiPEA (0.080 ml). After clarification, the solution was allowed to stir for 45 min at 0°C and for additional 16 hrs at room temperature. The solvent was eliminated by evaporation under reduced pressure and the residue was taken up with EtOAc (50 ml).

The organic solution was added with 5% $NaHCO_3$ aqueous solution (50 ml), and the resulting solution was allowed to stir for 20 min at room temperature. The organic phase was separated and extracted with a 5% $NaHCO_3$ aqueous solution (3 x 50 ml), with an NaCl saturated aqueous solution (3 x 50 ml), with a 0.1 N HCl aqueous solution (3 x

50 ml), and again with an NaCl saturated aqueous solution (3 x 50 ml). The organic phase, after water elimination on Na_2SO_4, was evaporated to dryness yielding a pale yellow residue (85 mg, yield 93%).

The two diastereoisomers were separated by reversed-phase 7 μ Lichrosorb ® RP-18 column (Hibar Merck ®) eluting with 48% acetonitrile aqueous mixture containing 0.1% trifluoroacetic acid. The fractions corresponding to the two peaks of the two isolated diastereoisomers were joined, concentrated to small volume at a reduced pressure and repeatedly freeze-dried.

HPLC analysis under isocratic conditions at 52% of A showed a single peak for each of the two products (denominated "fast" and "slow" depending on their being eluted at an earlier or, respectively, at a later time):

HPLC (fast) = 10.50 min HPLC (slow) = 11.03 min

EXAMPLE 2

N-methyl-N-benzylamide of N^{α}-{[N(indolin-3-yl-carbonyl)(R,L)-cis-2-amino]cyclohexanoyl}-L-phenylalanine and N-methyl-N-benzylamide of N^{α}-{[N(indolin-3-yl-carbonyl)(L,R)-cis-2-amino]cyclohexanoyl}-L-phenylalanine

1b) Methyl ester hydrochloride of cis-2-amino-cyclohexanecarboxylic acid (HCl,H-cis-2-Ac^6c-OMe)

Cis H-2-Ac^6c-OH (500 mg) was suspended, at room temperature, in a saturated solution of hydrochloric acid in methyl alcohol (7.5 ml). After 24-hr stirring at room temperature the solution was limpid.

The resulting solution was evaporated to dryness by nitrogen blowing; the residue was repeatedly taken up with methyl alcohol (4 x 15 ml) and evaporated to dryness for excess hydrochloric acid elimination.

The product was isolated by grounding with diethyl ether (3 x 10 ml). Yield 618 mg.

The R_f value obtained by thin layer chromatography (TLC) (eluent: CMA) was 0.25.

2b) Methyl ester of N-(indolin-3-yl-carbonyl)-cis-2-amino-cyclohexanecarboxylic acid (I3c-cis-2-Ac^{6}c-OMe)

A suspension of the product obtained under 1b) (500 mg) in DCM (5 ml) was cooled to 0°C, allowed to stir under nitrogen atmosphere, and added with 402 mg I3c-OH, 337 mg HOBt, 488 mg WSC, and 0.52 ml DiPEA. The limpid solution was allowed to stir for 45 min at 0°C and for additional 16 hrs at room temperature. The solvent was eliminated by evaporation under reduced pressure and the residue was taken up with EtOAc (50 ml). The organic solution was extracted with a 5% $NaHCO_3$ aqueous solution (3 x 50 ml), with an NaCl saturated aqueous solution (3 x 50 ml), with a 0.1 N HCl aqueous solution (3 x 50 ml), and again with an NaCl saturated aqueous solution (3 x 50 ml). The organic phase, after water elimination on Na_2SO_4, was evaporated to dryness. The residue was crystallized from ethyl alcohol/water to give a colourless microcrystalline product (610 mg, yield 85%).

HPCL was carried out as per 2) using 5μ Lichrospher® 100 RP-18 column (250 x 4.6 mm) and showed a single peak at R_t = 18.84 min.

The R_f value obtained by thin layer chromatography (TLC) (eluent: CM) was 0.23.

3b) N-(indolin-3-yl-carbonyl)-cis-2-amino-cyclohexanecarboxylic acid (I3c-cis-2-Ac^{6}c-OH)

A suspension of the product obtained under 2b) above (220 mg) in 5% NaOH (6.5 ml) was allowed to stir for 36 hrs at room temperature. The limpid solution was maintained at 0°C and under vigorous stirring, extracted with EtOAc (15 ml x 3) and acidified with 0.1 N HCl to pH 3.

The product was isolated by filtering the precipitate that forms and drying under reduced pressure (146 mg, yield 70%).

The R_f value obtained by thin layer chromatography (TLC) (eluent: chloroform/methyl alcohol, 80/20 v/v) was 0.50.

HPLC analysis as per step 2b showed a single peak at R_t = 14.83 min.

4b) N-methyl-N-benzylamide of N$^\alpha$-{[N(indolin-3-yl-carbonyl)(L,R)-trans-2-amino]cyclohexanoyl}-L-phenylalanine

and N-methyl-N-benzylamide of N$^\alpha$-{[N(indolin-3-yl-carbonyl)(R,L)-trans-2-amino]cyclohexanoyl}-L-phenylalanine

A suspension of the product obtained under 3b) above (70 mg) in DCM (7 ml) was cooled to 0°C, allowed to stir under nitrogen atmosphere, and added with HCl H-Phe-NMeBz (52 mg), PyBop (156 mg) and DiPEA (0.140 ml). The limpid solution was allowed to stir for 45 min at

0°C and for additional 16 hrs at room temperature. The solvent was eliminated by evaporation under reduced pressure and the residue was taken up with EtOAc (50 ml).

The organic solution was added with 5% $NaHCO_3$ aqueous solution (50 ml), and the resulting solution was allowed to stir for 20 min at room temperature. The organic phase was separated and extracted with a 5% $NaHCO_3$ aqueous solution (2 x 50 ml), with an NaCl saturated aqueous solution (3 x 50 ml), with a 0.1 N HCl aqueous solution (3 x 50 ml), and again with an NaCl saturated aqueous solution (3 x 50 ml). The organic phase, after water elimination on Na_2SO_4, was evaporated to dryness yielding a pale yellow residue (111 mg, yield 85%).

The two diastereoisomers were separated by reversed-phase 7 μ Lichrosorb ® RP-18 column (Hibar Merck ®) eluting with 44% acetonitrile aqueous mixture containing 0.1% trifluoroacetic acid.

The fractions corresponding to the two peaks of pure diastereoisomers were joined, concentrated to small volume at a reduced pressure and repeatedly freeze-dried.

HPLC analysis under isocratic conditions at 56% of A showed a single peak for each of the two products (denominated "fast" and "slow" depending on their being eluted at an earlier or, respectively, at a later time):

HPLC (fast) = 8.76 min HPLC (slow) = 10.96 min

The following compounds were also obtained:

N^{α}[N-(1H-indol-3-yl-carbonyl)-(R,S)cis-2-aminocyclohexyl-carbonyl]-L-3(2-naphthyl)alanyl-N-methyl-N-benzylamide and N^{α}[N-(1H-indol-3-yl-carbonyl)-(S,R)cis-2-aminocyclohexyl-carbonyl]-L-3(2-naphthyl)alanyl-N-methyl-N-benzylamide;

HPLC: column Phase Sep.

Spherisorb ODS-2 5mm (250x4.6 mm) fitted with a Phase Sep. Spherisorb S5 ODS-2 (50x4.6 mm) precolumn; eluent A: H_2O, 0.1% trifluoroacetic acid; eluent B:

Acetonitrile, 0.1% trifluoroacetic acid; UV Detection 215 nm; flow 1 ml/min; linear gradient from 20% to 80% B in 20 min, then isocratic 80% B for 10 min (HPLC System 1):

fast: T_R = 7.66 min slo T_R = 8.69 min;

TLC(SiO_2)$CHCl_3/CH_3OH$ (9:1 v/v) R_f = 0.4 and 0.4

N^{α}[N-(1H-indol-3-yl-carbonyl)-(R,S)cis-2-aminocyclohexyl-carbonyl]-L-2-phenylalanyl-N-benzylamide and N^{α}[N-(1H-indol-3-yl-carbonyl-(S,R)cis-2-aminocyclohexyl-carbonyl]-L-2-phenylalanyl-N-benzylamide;

HPLC: column Phase Sep. Spherisorb ODS-2 5 mm (250 x 4.6 mm) fitted with a Phase Sep. Spherisorb S5 ODS-2 (50 x 4.6 mm) precolumn; eluent A: H_2O, 0.1% trifluoroacetic acid; eluent B: Acetonitrile, 0.1% trifluoroacetic acid; UV Detection 215 nm; flow 1 ml/min; (HPLC system 2) isocratic 59% B;

fast: T_R = 7.66 min slow T_R = 8.69 min;

TLC(SiO_2)CH_2Cl_2/CH_3OH (95:5 v/v) R_f = 0.17 and 0.17

N^{α}[N-(1H-indol-3-yl-carbonyl)-(R,S)cis-2-aminocyclohexyl-carbonyl]-L-phenylalanyl-N,N dibenzylamide and N^{α}[N-(1H-indol-3-yl-carbonyl) -(S,R)cis-2-aminocyclohexan-carboxyl]-L-phenylalanyl-N,N dibenzylamide;
HPLC: (System 2) isocratic 66% B;
fast: T_R = 13.94 min slow T_R = 15.16 min;
TLC(SiO_2)CH_2Cl_2/CH_3OH (95:5 v/v) R_f = 0.23 and 0.31

N^{α}[N-(1-(methyl)indol-3-yl-carbonyl)-(R,S)cis-2-aminocyclohexyl-carbonyl]-L-3(2-naphthyl)alanyl-N-methyl-N-benzylamide and N^{α}[N-(1-(methyl)indol-3-yl-carbonyl)-(S,R)cis-2-aminocyclohexyl -carbonyl]-L-3(2-naphthyl)alanyl-N-methyl-N-benzylamide;
HPLC:(System 1) fast: T_R = 13.94 min slow T_R = 15.16 min;
TLC(SiO_2) CH_2Cl_2/CH_3OH (95:5 v/v) R_f = 0.23 and 0.31

N^{α}[N-(1-(methyl)indol-3-yl-carbonyl)-(R,S)cis-2-aminocyclohexyl-carbonyl]-L-phenylalanyl-N-methyl-N-benzylamide;
HPLC: (System 2) isocratic 70% B;
T_R = 9.94 min
TLC(SiO_2) $CHCl_3/CH_3OH$ (90:10 v/v) R_f = 0.65

N^{α}[N-(1H-indol-3-yl-carbonyl)-(R,S)cis-2-aminocyclohexyl-carbonyl]-L-phenylalanyl-N,N dimethylamide and N^{α}[N-(1H-indol-3-yl-carbonyl) -(S,R)cis-2-aminocyclohexan-carbonyl]-L-phenylalanyl-N,N dimethylamide;
HPLC: (System 2) isocratic 52% B;
fast: T_R = 7.36 min slow T_R = 9.70 min;

N^{α}[N-(1H-indol-3-yl-carbonyl)-(R,S)cis-2-aminocyclohexyl-carbonyl]-L-phenylalanyl-tetrahydroisoquinolide and N^{α}[N-(1H-indol-3-yl-carbonyl) -(S,R)cis-2-aminocyclohexan-carboxyl]-L-phenylalanyl-tetrahydroisoquinolide;

HPLC: (System 2) isocratic 65% B;

fast: T_R = 8.71 min slow T_R = 10.74 min;

N^{α}[N-(1H-indol-3-yl-carbonyl)-3S-endo aminobicyclo(2,2,1)heptyl-2R endo carbonyl]-L-3-(2-naphthyl)alanyl-N-methyl-N-benzylamide and N^{α}[N-(1H-indol-3-yl-carbonyl)-3R-endo aminobicyclo(2,2,1)heptyl-2S-endo carbonyl]-L-3-(2-naphthyl)alanyl-N-methyl-N-benzylamide;

HPLC: (System 2) isocratic 60% B;

fast: T_R = 14.39 min slow T_R = 15.54 min;

N^{α}[N-(1H-indol-3-yl-carbonyl)-3S-exo-aminobicyclo(2,2,1)heptyl- 2R-exo carbonyl]-L-3-(2-naphthyl)alanyl-N-methyl-N-benzylamide and N^{α}[N-(1H-indol-3-yl-carbonyl)-3R-endo aminobicyclo(2,2,1) heptyl -2S-exo carbonyl]-L-3-(2-naphthyl)alanyl-N-methyl-N-benzylamide;

HPLC: (System 2) isocratic 70% B;

fast: T_R = 9.20 min slow T_R = 11.87 min;

N^{α}[N-(1H-indol-3-yl-carbonyl)-(R,S)cis-2-amino(3,4 dehydro) cyclohexyl-carbonyl]-L-3(2-naphthyl)alanyl-N-methyl-N-benzylamide and N^{α}[N-(1H-indol-3-yl-carbonyl)-(S,R)cis-2-amino (3,4 dehydro) cyclohexyl-carbonyl]-L-3-(2-naphthyl)alanyl-N-

methyl-N-benzylamide;

HPLC: (System 1)

fast: T_R = 26.42 min slow T_R = 27.38 min;

TLC(SiO_2) $CHCl_3/CH_3OH$ (9:1 v/v) R_f = 0.43 and 0.43

N^{α}[N-(1H-indol-3-yl-carbonyl)-(R,S)cis-2-aminocyclohexyl-carbonyl]-L-2 phenylglicyl-N-methyl-N-benzylamide and N^{α}[N-(1H-indol-3-yl-carbonyl)-(S,R)cis-2-aminocyclohexyl-carbonyl]-L-2 phenylglicyl-N-methyl-N-benzylamide;

HPLC: (System 2) isocratic 60% B:

fast: T_R = 9.26 min slow T_R = 10.90 min;

N^{α}[N-(1H-indol-3-yl-carbonyl)-(R,S)cis-2-aminocyclohexyl-carbonyl]-L-3-Cyclohexyl alanyl-N-methyl-N-benzylamide and N^{α}[N-(1H-indol-3-yl-carbonyl)-(S,R)cis-2-aminocyclohexyl carbonyl]-L-3 Cyclohexyl alanyl-N-methyl-N-benzylamide;

HPLC: (System 2) isocratic 45% B:

fast: T_R = 8.26 min slow T_R = 15.26 min;

N^{α}[N-(1H-indol-3-yl-carbonyl)-(R,S)cis-2-aminocyclohexyl-carbonyl]-L-3-(1-naphthyl)alanyl-N-methyl-N-benzylamide and N^{α}[N-(1H-indol-3-yl-carbonyl)-(S,R)cis-2-aminocyclohexyl-carbonyl]-L-3-(1-naphthyl)alanyl-N-methyl-N-benzylamide;

HPLC: (system 2) isocratic 60% B:

fast: T_R = 10.22 min slow T_R = 11.96 min;

N^{α}[N-(1H-indol-3-yl-carbonyl)-(R,S)cis-2-aminocyclohexyl-carbonyl]-D-3-(2-naphthyl)alanyl-N-methyl-N-benzylamide and N^{α}[N-(1H-indol-3-yl-carbonyl)-(S,R)cis-2-aminocyclohexyl-carbonyl]-D-3-(2-naphthyl)alanyl-N-methyl-N-benzylamide;

HPLC: (System 2) isocratic 45% B:

fast: T_R = 8.26 min slow T_R = 15.26 min;

N^{α}[N-(benzoyl)-(R,S)cis-2-aminocyclohexyl-carbonyl]-D-3-(2-naphthyl)alanyl-N-methyl-N-benzylamide and N^{α}[N-(benzoyl)-(S,R)cis-2-aminocyclohexyl-carbonyl]-D-3-(2-naphthyl)alanyl-N-methyl-N-benzylamide;

HPLC: (System 2) isocratic 70% B:

fast: T_R = 11.06 min slow T_R = 18.82 min;

Assessment of biological activity (NK1 antagonism) of compounds of this invention was performed by means of the following binding and functional assays:

[3H] SP binding assay in IM9 Cell Line

Binding assay was performed with intact cells as described by Payan et al. (J. Immunology 133, 3260 (1984)). Cells were washed with buffer A, (pH 7.5), containing (in mM) Tris-HCl 50, and NaCl 150, plus 0.02 % BSA, and then resuspended in assay buffer (buffer A supplemented with protease inhibitors) at a concentration of 1 x 10^7 cells/ml. Cells were incubated with [^{3}H]SP in a final volume of 0.5 ml for 60 min. at room temperature. Nonspecific binding was

determined in the presence of 10 mM nonradioactive SP. The assay mixture was set up in microfuge tubes that had been presoaked in a 0.5% BSA solution for at least 3 hours. Bound and free [^{3}H]SP were separated by pelleting the cells in a microfuge (6 min.; 12000 g); the supernatant was then removed by aspiration. For competition binding experiments, IM9 cells were incubated in triplicate with 0.3 nM [^{3}H]SP (the approximate Kd value, as determined in saturation binding experiments); competing ligands were tipically added in six concentrations (1:10 dilutions in assay buffer) to give full competition curves.

Measurement of pA_2 in isolated guinea pig ileum

Male albino guinea-pigs weighing 300-350 g were stunned and bled. A segment of ileum was excised and placed in oxygenated Krebs solution containing 10 mM indomethacin. The longitudinal muscle with attached myenteric plexus was then removed, the longitudinal muscle-myenteric plexus was discarded and a ring approximately 3 mm wide was excised and used for subsequent experiments. Ileal rings were suspended in 5-ml organ baths by means of two stainless steel hooks and connected to an isotonic transducer (load 5 mN). After 90 min. equilibration period a cumulative concentration-response curve for the agonist, [Sar^9] substance P sulfone was made. After two or more reproducible control curves for the agonist had been obtained, the compound to be tested was added to the bath and a new curve for the agonist was determined in its presence.

Regression analysis was performed by the least-squares method. EC_{50}

values and 95% confidence limits (c.I.) were calculated. Schild plots were constructed and if the slope was not significantly different from unity, pA_2 values were calculated by using the constrained Schild plot method.

The data in Table I were obtained for compound of formula (I):

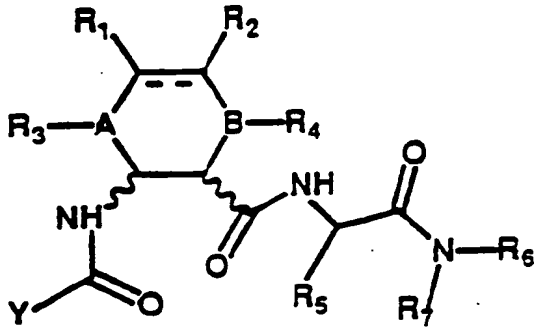
Table I

Substance P antagonism Results

Compound of Ex #	% of binding inhibition at 1μM
1 fast	96%
2 fast	100%
3 fast	100%
10 fast	95%
17 fast	98%

CLAIMS

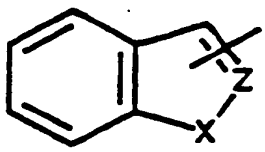
1. A tachyquinine antagonist compound having general formula (I)



(I)

wherein:

Y is selected out of a group consisting of hydrogen, a linear or branched alkyl radical containing 1 to 6 carbon atoms, a linear or branched alkenyl radical containing 2 to 7 carbon atoms, a linear or branched alkynyl radical containing 3 to 7 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, possibly substituted with at least one atom selected out of a group consisting of N, S, and O, an aryl-, aryl-alkyl-, alkyl-aryl- radical containing 7 to 12 carbon atoms, a radical of type



where X stands for O, S, CH_2, NH or N-R_8 where R_8 is selected out of a group consisting of H, a linear or branched alkyl radical containing 1 to 6 carbon atoms, a linear or branched alkenyl radical

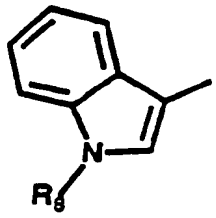
containing 2 to 7 carbon atoms, a linear or branched alkynyl radical containing 3 to 7 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, possibly substituted with at least one atom selected out of a group consisting of N, S, and O, an aryl-, aryl-alkyl-, alkyl-aryl- radical containing 7 to 12 carbon atoms, and Z = CH or N, each with suitable substituents;

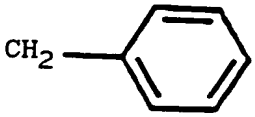
symbol --- represents a single or a double bond: if the bond is single, R_1 and R_2 are selected out of a group consisting of hydrogen, hydroxyl and halogen or are joined to form an epoxide; if the bond is double, they are hydrogen or halogen; A and B stand for N or CH; R_3 and R_4 are selected out of the group consisting of hydrogen, a linear or branched alkyl radical containing 1 to 6 carbon atoms, a linear or branched alkenyl radical containing 2 to 7 carbon atoms, a linear or branched alkynyl radical containing 3 to 7 carbon atoms, or are joined together to form a $-(CH_2)_n-$ bridge, where n stands for a whole number from 1 to 3;

R_5 stands for an alkyl-, aryl-, aryl-alkyl-, alkyl-aryl- radical with 15 carbon atoms max.;

R_6 and R_7 are selected out of a group consisting of hydrogen, an alkyl -, aryl-, aryl-alkyl-, alkyl-aryl- radical, and where symbol ∿∿∿ means that the configuration of the asymmetric carbon atoms of 2-amino-cyclohexanecarboxylic acid is S or R.

2. The compound according to claim 1, wherein

Y = 

3. The compound according to claim 2, wherein R_8 = H; R_5 and R_6 = 

and the configuration of the asymmetric carbon atoms of 2-amino cyclohexanecarboxylic acid is S or R.

4. The compound according to claims 1 to 3, wherein the alkyl radical is selected out of the group consisting of methyl, ethyl, propyl, butyl, and pentyl; the alkenyl radical is selected out of the group consisting of propenyl and butenyl; the alkynyl radical is propynyl; aryl- alkyl-aryl- and aryl-alkyl-radicals present an alkyl radical as defined above, while the aryl moiety is selected out of the group consisting of possibly substituted pyridine, benzofuran, benzene, indole, naphthyl, tetrahydroquinoline, imidazole, tetrahydroindoline; a cycloalkyl radical, possibly substituted is selected out of a group consisting of cyclohexane, cyclopentane, cycloheptane, cyclooctane, piperidine, morpholine, piperazine, and pyrazine.

5. Compounds of formula (I) represented by:

N-methyl-N-benzylamide of N^{α}-{[N(indolin-3-yl-carbonyl)(R,R)-trans-2-amino]cyclohexanoyl}-L-phenylalanine and N-methyl-N-benzylamide of N^{α}-{[N(indolin-3-yl-carbonyl)(L,L)-trans-2-amino]cyclohexanoyl}-L-phenylalanine;

N-methyl-N-benzylamide of N^{α}-{[N(indolin-3-yl-carbonyl)(R,L)cis-2-amino]cyclohexanoyl}-L-phenylalanine and N-methyl-N-benzylamide of N^{α}-{[N(indolin-3-yl-carbonyl)(L,R)cis-2-amino]cyclohexanoyl}-L-phenylalanine;

N^{α}[N-(1H-indol-3-yl-carbonyl)-(R,S)cis-2-aminocyclohexyl-carbonyl]-L-3(2-naphthyl)alanyl-N-methyl-N-benzylamide and N^{α}[N-(1H-inodol-3-yl-carbonyl)-(S,R)cis-2-aminocyclohexyl-carbonyl]-L-3(2-naphthyl)alanyl-N-methyl-N-benzylamide;

N^{α}[N-(1H-indol-3-yl-carbonyl)-(R,S)cis-2-aminocyclohexyl-carbonyl]-L-2-phenylalanyl-N-benzylamide and N^{α}[N-(1H-indol-3-yl-carbonyl-(S,R)cis-2-aminocyclohexyl-carbonyl]-L-2-phenylalanyl-N-benzylamide;

N^{α}[N-(1H-indol-3-yl-carbonyl)-(R,S)cis-2-aminocyclohexyl-carbonyl]-L-phenylalanyl-N,N dibenzylamide and N^{α}[N-(1H-indol-3-yl-carbonyl) -(S,R)cis-2-aminocyclohexan-carboxyl]-L-phenylalanyl-N,N dibenzylamide;

N^{α}[N-(1-(methyl)indol-3-yl-carbonyl)-(R,S)cis-2-aminocyclohexyl-carbonyl]-L-3(2-naphthyl)alanyl-N-methyl-N-benzylamide and N^{α}[N-(1-(methyl)indol-3-yl-carbonyl)-(S,R)cis-2-aminocyclohexyl-carbonyl]-L-3(2-naphthyl)alanyl-N-methyl-N-benzylamide;

N^{α}[N-(1-(methyl)-indol-3-yl-carbonyl)-(R,S)cis-2-aminocyclohexyl-carbonyl]-L-phenylalanyl-N-methyl-N-benzylamide;

N^{α}[N-(1H-indol-3-yl-carbonyl)-(R,S)cis-2-aminocyclohexyl-carbonyl]-L-phenylalanyl-N,N dimethylamide and N^{α}[N-(1H-indol-3-yl-carbonyl) -(S,R)cis-2-aminocyclohexan-carboxyl]-L-phenylalanyl-N,N dimethylamide;

N^{α}[N-(1H-indol-3-yl-carbonyl)-(R,S)cis-2-aminocyclohexyl-carbonyl]-L-phenylalanyl-tetrahydroisoquinolide and N^{α}[N-(1H-indol-3-yl-carbonyl) -(S,R)cis-2-aminocyclohexan-carboxyl]-L-phenylalanyl-tetrahydroisoquinolide;

N^{α}[N-(1H-indol-3-yl-carbonyl)-3S-endo aminobicyclo(2,2,1)heptyl-2R endo carbonyl]-L-3-(2-naphthyl)alanyl-N-methyl-N-benzylamide and N^{α}[N-(1H-indol-3-yl-carbonyl)-3R-endo aminobicyclo(2,2,1)heptyl -2S-endo carbonyl]-L-3-(2-naphthyl)alanyl-N-methyl-N-benzylamide;

N^{α}[N-(1H-indol-3-yl-carbonyl)-3S-exo-aminobicyclo(2,2,1)heptyl- 2R-exo carbonyl]-L-3-(2-naphthyl)alanyl-N-methyl-N-benzylamide and N^{α}[N-(1H-indol-3-yl-carbonyl)-3R-endo aminobicyclo(2,2,1) heptyl -2S-exo carbonyl]-L-3-(2-naphthyl)alanyl-N-methyl-N-benzylamide;

N^{α}[N-(1H-indol-3-yl-carbonyl)-(R,S)cis-2-amino(3,4 dehydro) cyclohexyl-carbonyl]-L-3(2-naphthyl)alanyl-N-methyl-N-benzylamide and N^{α}[N-(1H-indol-3-yl-carbonyl)-(S,R)cis-2-amino (3,4 dehydro) cyclohexyl-carbonyl]-L-3-(2-naphthyl)alanyl-N-methyl-N-benzylamide;

N^{α}[N-(1H-indol-3-yl-carbonyl)-(R,S)cis-2-aminocyclohexyl-carbonyl]-L-2 phenylglicyl-N-methyl-N-benzylamide and N^{α}[N-(1H-indol-3-yl -carbonyl)-(S,R)cis-2-aminocyclohexyl-carbonyl]-L-2 phenylglicyl-

N-methyl-N-benzylamide;

N^{α}[N-(1H-indol-3-yl-carbonyl)-(R,S)cis-2-aminocyclohexyl-carbonyl]-L-3-Cyclohexyl alanyl-N-methyl-N-benzylamide and

N^{α}[N-(1H-indol-3-yl-carbonyl)-(S,R)cis-2-aminocyclohexyl carbonyl]-L-3 Cyclohexyl alanyl-N-methyl-N-benzylamide;

N^{α}[N-(1H-indol-3-yl-carbonyl)-(R,S)cis-2-aminocyclohexyl-carbonyl]-L-3-(1-naphthyl)alanyl-N-methyl-N-benzylamide and

N^{α}[N-(1H-indol-3-yl-carbonyl)-(S,R)cis-2-aminocyclohexyl-carbonyl]-L-3-(1-naphthyl)alanyl-N-methyl-N-benzylamide;

N^{α}[N-(1H-indol-3-yl-carbonyl)-(R,S)cis-2-aminocyclohexyl-carbonyl]-D-3-(2-naphthyl)alanyl-N-methyl-N-benzylamide and

N^{α}[N-(1H-indol-3-yl-carbonyl)-(S,R)cis-2-aminocyclohexyl-carbonyl]-D-3-(2-naphthyl)alanyl-N-methyl-N-benzylamide;

N^{α}[N-(benzoyl)-(R,S)cis-2-aminocyclohexyl-carbonyl]-D-3-(2-naphthyl)alanyl-N-methyl-N-benzylamide and N^{α}[N-(benzoyl)-(S,R)cis-2-aminocyclohexyl-carbonyl]-D-3-(2-naphthyl)alanyl-N-methyl-N-benzylamide.

6. Pharmaceutical composition containing, as active ingredient, an effective dose of compound as per formula 1 according to claim 1.

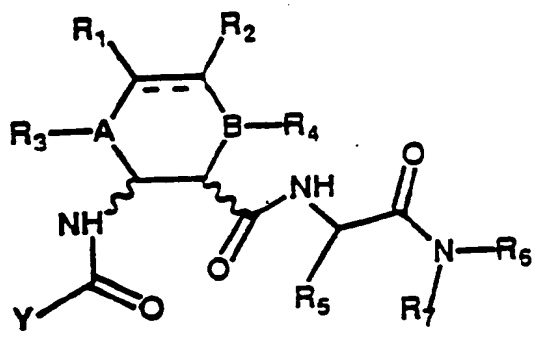
7. Pharmaceutical composition containing, as active ingredient, an effective dose of compound according to claim 2.

8. Pharmaceutical composition containing, as active ingredient, an effective dose of compound according to claim 3.

9. Use of compounds of formula (I) according to claims 1, 2, 3, and 4, as active ingredients for the preparation of pharmaceutical

compositions.

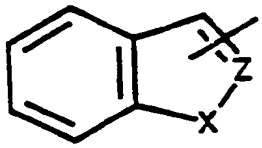
10. Process for the preparation of tachyquinine antagonist compound having general formula (I)



(I)

wherein:

Y is selected out of a group consisting of hydrogen, a linear or branched alkyl radical containing 1 to 6 carbon atoms, a linear or branched alkenyl radical containing 2 to 7 carbon atoms, a linear or branched alkynyl radical containing 3 to 7 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, possibly substituted with at least one atom selected out of a group consisting of N, S, and O, an aryl-, aryl-alkyl, alkyl-aryl radical containing 7 to 12 carbon atoms, a radical of type



where X stands for O, S, CH_2, NH or N-R_8 where R_8 is selected out of a group consisting of H, a linear or branched alkyl radical containing 1 to 6 carbon atoms, a linear or branched alkenyl radical containing 2 to 7 carbon atoms, a linear or branched alkynyl radical containing 3 to 7 carbon atoms, a cycloalkyl radical containing 3 to 6 carbon atoms, possibly substituted with at least one atom selected out of a group consisting of N, S, and O, an aryl-, aryl-alkyl-, alkyl-aryl radical containing 7 to 12 carbon atoms, and Z = CH or N, each with suitable substituents;

symbol --- represents a single or a double bond: if the bond is single, R_1 and R_2 are selected out of a group consisting of hydrogen, hydroxyl and halogen or are joined to form an epoxide; if the bond is double, they are hydrogen or halogen; A and B stand for N or CH; R_3 and R_4 are selected out of the group consisting of hydrogen, a linear or branched alkyl radical containing 1 to 6 carbon atoms, a linear or branched alkenyl radical containing 2 to 7 carbon atoms, a linear or branched alkynyl radical containing 3 to 7 carbon atoms, or are joined together to form a -$(CH_2)_n$- bridge, where n stands for a whole number from 1 to 3;

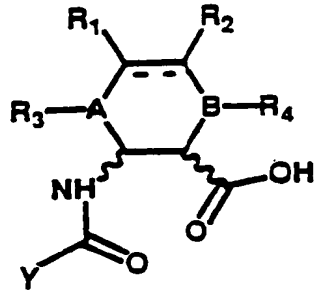
R_5 stands for an alkyl, aryl, aryl-alkyl, alkyl-aryl radical with 15 carbon atoms max.;

R_6 and R_7 are selected out of a group consisting of hydrogen, an alkyl, aryl, aryl-alkyl, alkyl-aryl radical, and where symbol ∿∿∿ means that the configuration of the asymmetric carbon atoms

of 2-amino-cyclohexanecarboxylic acid is S or R,

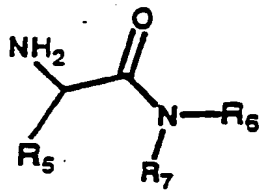
via the steps of:

a) condensing, in the presence of a suitable condensing agent, intermediate of formula (II)



(II)

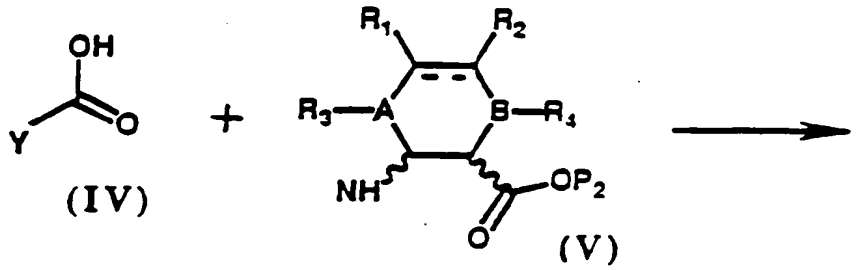
with intermediate of formula (III)



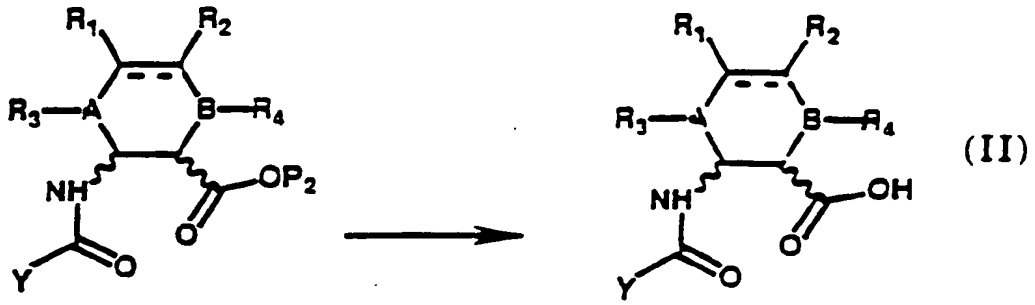
(III)

where R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, A, and B are as defined above, said compound of formula (II) being prepared by condensation, in the presence of a suitable condensing agent, of compound of general formula (IV) with a derivative of the acid of general formula (V), suitably substituted on the ring, followed by elimination of the

carboxylic end group

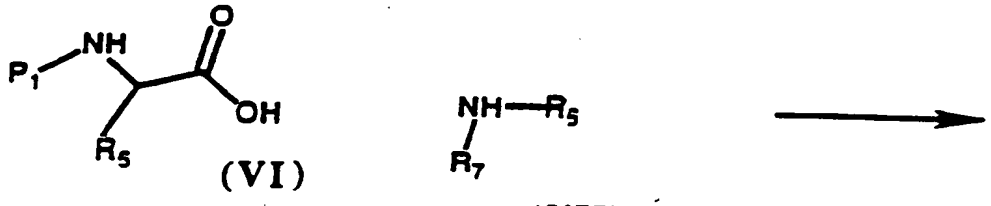


(IV) (V)

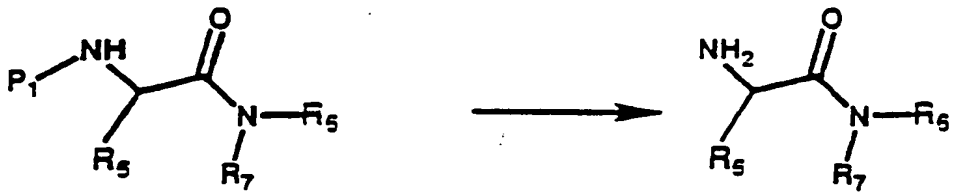


(II)

where R_1, R_2, R_3, R_4, R_8, A, and B are as defined above and P_2 is a group that temporarily protects the carboxylic group, and intermediates of general formula (III) being prepared by condensation of amino acid derivative of general formula (VI) and amine of general formula (VII)



(VI) (VII)



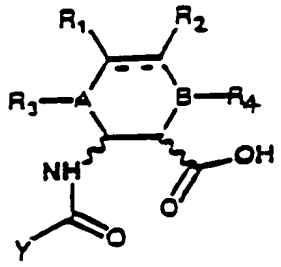
(III)

where R_5, R_6, R_7, R_8 are as defined above and P_1 is a group protecting the α-amino group, selected out of the groups commonly used in classical peptide syntheses, which can be easily removed under conditions not causing the partial or total opening of the bond between R_6, R_7 and nitrogen, said condensation being carried out in the presence of aprotic polar organic solvents;

b) eliminating the reaction by-products by evaporation of the reaction solvent and treatment of the residue, or a solution of same in a suitable organic solvent, with slightly acid or slightly basic aqueous solutions;

c) separating the residue obtained under b) by chromatography or crystallization.

11. Compounds of general formula (II)



(II)

where R_1, R_2, R_3, R_4, A, B and Y are as defined in claim 1.

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP 93/03387

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: C07K 5/02, A61K 37/42
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: A61K, C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EMBASE, MEDLINE, WPI, CHEMICAL ABSTRACTS, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 5164372 (MATSUO, M. ET AL), 17 November 1992 (17.11.92) --	1-10
A	EP, A, 0482539 (FUJISAWA PHARMACEUTICAL CO. LTD.), 29 April 1992 (29.04.92) --	1-10
P,A	WO, A1, 9314113 (FUJISAWA PHARMACEUTICAL CO., LTD.), 22 July 1993 (22.07.93) --	1-10

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 March 1994	25. 04. 94

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	ELISABETH CARLBORG

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INTERNATIONAL SEARCH REPORT

Information on patent family members

26/02/94

International application No.
PCT/EP 93/03387

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 5164372	17/11/92	EP-A- 0394989	31/10/90
		JP-A- 3027399	05/02/91
EP-A- 0482539	29/04/92	AU-A- 8592591	30/04/92
		CN-A- 1060848	06/05/92
		JP-A- 4297492	21/10/92
WO-A1- 9314113	22/07/93	NONE	